non-invasively treating the particular volume of tissue with light to promote thermal overload of pigmented cells in the particular volume of tissue, wherein said thermal overload kills said pigmented cells.

REMARKS

Applicants have the following response to the Office Action of May 8, 2001.

Applicants appreciate the Examiner's allowance of Claims 75-77. Applicants also appreciate the Examiner's statement that Claims 1-36 and 97-107 contain allowable subject matter. Applicants respectfully submit that Claims 37-54 should also be included in this category as none of these claims has been rejected under §102 or §103.

Applicants will now address each item listed in the office action in the order in which they appear.

I. ELECTION / RESTRICTIONS

Applicants affirm the election to prosecute Claims 1-77 and 97-107 in the above-identified application. Applicants are making this election without prejudice to pursuing the non-elected claims in a divisional application.

II. DOUBLE PATENTING

The Examiner rejects Claims 1-11, 13-15, 19-29, 31-33 and 37-51 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-6, 8, 10-15, 17, 19, 20, 29-34, 40-45, 52-55, 60 and 62-67 of U.S. Patent No. 5,829,448. The Examiner further rejects Claims 1-6 and 19-24 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 10, 13, 14, 17-20 and 23 of U.S. Patent No. 5,998,597. Finally,

the Examiner provisionally rejects Claims 37-42, 45-52 and 54 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 73-75, 82-84, 89, 90, 92, 99, 85-87 and 79 of co-pending application no. 09/096,832.

Three terminal disclaimers and the corresponding fees are being filed herewith. Accordingly, it is respectfully submitted that this rejection has now been overcome.

If any additional fee should be due for these terminal disclaimers, please charge our deposit account 50/1039.

II. CLAIM REJECTIONS - 35 USC §102/103

A. Rejection Over Daikuzono, et al.

The Examiner also has rejects Claims 55-69 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Daikuzono et al. (USP 5,050,597). Applicants vigorously but respectfully traverse this rejection for a number of reasons, as discussed below.

Independent Claim 55 of the present application, as amended, is directed to a method for the treatment of a particular volume of tissue, said volume of tissue containing an endogenous pigment, the method comprising the steps of: non-invasively treating the particular volume of tissue with light to promote thermal overload of pigmented cells in the particular volume of tissue, wherein said thermal overload kills said pigmented cells. As explained in depth below, Daikuzono is clearly different than the claimed invention as, at a minimum, this reference is directed to an invasive technique which uses exogeneous photosensitizers. Hence, the reference does not disclose or suggest the method of independent Claim 55 or those claims dependent thereon.

More specifically, Figure 6 in Daikuzono illustrates that the apparatus in this reference concerns an *invasive light application device* for laser thermotherapy:

> FIG. 6 is a sectional view showing the probe as *the laser beam emitting end and the temperature sensor* which *are inserted into the tissue*; (Col. 4, lines 41-43, emphasis added)

In the Abstract, Daikuzono states that this apparatus comprises:

> Laser thermotherapy apparatus including a laser splitter which branches laser energy from a laser source to laser guides or optical fibers, each guide having an *emitting end.... Temperature sensors* are provided to *sample the temperature of living tissue located adjacent each guide emitting end.* (Abstract, emphasis added)

Those of ordinary skill in the art would clearly understand that such apparatus, as illustrated in Figure 6, is intended for insertion into tissue, and thus is an invasive device. Further, it is clear that any significant illumination of tissue below the tissue surface would occur only upon such insertion of such apparatus.

The salient features of the apparatus in Daikuzono are further described by the Summary of the Invention:

> To solve the problems as described above and to achieve the objects as described above, the first invention features a *laser irradiation system for thermotherapy* which *comprises laser beam guides* for guiding laser beam to a *plurality of laser beam emitting ends*; ... temperature sensing means provided in combination with the respective laser beam emitting ends for detecting temperatures of a living tissue.... (Col. 2, lines 7-14, emphasis added)
>
> The second invention features a *laser irradiation system for thermotherapy* which *comprises laser beam guide means* through which a laser beam is branched to a plurality of laser beam emitting ends; ... temperature sensing means provided in combination with the respective laser beam emitting ends for detecting temperatures of a living tissue .... (Col. 2, lines 18-28, emphasis added)
>
> Further, the third invention features a *laser irradiation system for thermotherapy* which *comprises laser beam guide means* through

> which a laser beam is branched to a plurality of laser beam emitting ends; ... temperature sensing means provided in combination with the respective laser beam emitting ends after the branching for detecting temperatures of a living tissue .... (Col. 2, lines 32-46, emphasis added)
>
> The fourth invention features a *laser irradiation system for thermotherapy* which *comprises laser beam guide means* through which a laser beam is branched to a plurality of laser beam emitting ends; ... temperature sensing means provided in combination with the respective laser beam emitting ends after the branching for detecting temperatures of a living tissue.... (Col. 2, lines 51-66, emphasis added)

Thus, the "invention(s)" in Daikuzono require, in general, a laser irradiation system for thermotherapy.

This apparatus is further described by Figure 1 and the description thereof in which Daikuzono states that:

> The main guide ... is branched into, for example, four branch guides.... *Each of the branch guides ... has, at its respective tip end, a probe* ... at which the laser beam emits. The main guide ... and the branch guides ... are each made of a flexible optical fiber ... and the probe ... is provided at each of the tip ends of the respective optical fibers coaxially therewith. (Col. 5, lines 4-11, emphasis added)

Thus, the system in Daikuzono requires a laser irradiation system for thermotherapy wherein a light delivery probe emits therapeutic laser light. This probe, as illustrated in Figure 6, is *inserted into tissue* so as to allow illumination of tissue below the tissue surface.

Daikuzono continues by noting that the apparatus can be used without such probe, but that use of the invasive probe is clearly preferred:

> Of course, the tip end of the optical fiber itself may be used as a laser beam emitting end, but *it is preferred to employ the probe to puncture a tissue.* (Col. 5, lines 11-14, emphasis added)[1]

For the preferred use with a probe, Daikuzono provides a detailed description:

> An example of a particular configuration of the probe ... is as illustrated in FIG. 3. The probe ... may preferably be *made of a laser-transmittable material* such as natural or artificial sapphire, quartz, diamond, or other natural or artificial ceramic material. Or, the probe ... may be made of some polymeric material. The probe ... is *preferably comprised of a tapering conical puncturing portion* ..., a fixing portion ... and a flange portion ... provided therebetween. (Col. 5, lines 27-36, emphasis added)

Thus, it is clear that the preferred embodiment in Daikuzono is for such probe to deliver light into tissue upon puncturing such tissue with such probe.

Moreover, as further described by this passage (and illustrated by Figures 1 and 4- 8), the apparatus in Daikuzono also includes not only an inserted light applicator (i.e., fiberoptic light guide terminated with a tapered puncturing probe) but also one or more inserted temperature monitoring probes:

> Temperature sensors ... comprising a thermocouple are provided for the respective branch guides ... and/or probes ... at positions adjacent to the probes, respectively. (Col. 5, lines 14-17)

Thus, the apparatus in Daikuzono requires not only one or more invasive light delivery probes but also one or more invasive temperature monitoring probes.

Although details concerning intended use of the apparatus in Daikuzono are sparse, the Background of the Invention in Daikuzono provides some insight:

---

[1]It is unclear from the remaining disclosure how the apparatus in Daikuzono might be used without a probe. Applicants could speculate as to how this could be done, but such speculation is well beyond the disclosure and does not meet the test for a sufficient disclosure under §112.

> This invention relates to a laser irradiating *apparatus for thermotherapy*
>
> Recently, [In thermotherapy], laser beam is irradiated for 10 to 25 minutes to keep a cancer tissue at a temperature of 42° to 44°C. for letting the tissue die. The effectiveness of this therapy has been reported, by N. Daikuzono ....
>
> In this case, a single *probe is used for emitting laser beam* generated by a laser beam generator and it *is inserted in a tissue to be treated*, while the laser beam is irradiated from the probe. At the same time, to keep the tissue temperature at a temperature of 42° to 44°C., a tip end of *a temperature sensor paired with the probe is also inserted in the tissue* to measure the tissue temperature and control the on-off operation of a shutter provided in a laser beam guide system which connects the laser beam generator and the probe. (Col. 1, lines 9-31, emphasis added)

Thus, according to Daikuzono, laser thermotherapy is an invasive procedure. Further insight into the laser thermotherapy technique and the apparatus and method in Daikuzono is provided in the Summary of the Invention:

> However, in the conventional local thermotherapy, a single pair of laser beam probe and temperature sensor is employed. Therefore, a temperature distribution in the tissue caused by laser beam irradiation forms a convex around the probe as shown in FIG. 10..... This makes the temperature control of the living tissue very difficult.
>
> It is therefore an object of the present invention to provide a laser beam irradiation system which is capable of effecting thermotherapy for a wide region.... (Col. 1, lines 46-66)

Hence, as described *supra*, Daikuzono describes an apparatus that utilizes a multiplicity of light delivery probes and temperature sensors to effect thermotherapy over a wider region than is possible using conventional, single probe thermotherapy apparatus.

Daikuzono also suggests that this apparatus may be usable for both thermotherapy and for excitation of certain photosensitizers:

> In a further preferred form of the present invention, thermotherapy is carried out in combination with a medical treatment by a photochemical reaction, using a single laser beam generator, which has never been practiced before. The *laser beam suitable* for the *photochemical reaction is preferably* a pulsive laser beam having a *pulse duration of about 10 nanosec* and having an exciting energy as large as 10 mJ as a fundamental wave of 1.064 um wavelength and 0.5 mJ as a subharmonic wave (SH wave) of 532 nm wavelength .... This enables the laser beam emitting ends of the respective guides to irradiate laser beam optimum for the photochemical reaction, causing two-photon absorbing reaction sufficiently within the tissue. (Col. 3, line 67 to Col. 4, line 16, emphasis added)

Further:

> This pulsive laser beam employable in the present invention has preferably high peaks of 30 W or more, so as also to cause a photochemical reaction. (Col. 5, lines 1-3)

And:

> However, it is to be noted that the photochemical reaction can not be used in combination with this continuous oscillation method. (Col. 7, lines 22-24)

Thus, the teaching in Daikuzono also includes use of the thermotherapy apparatus to excite certain photochemical reactions. Such excitation is alleged to occur only upon use of a pulsed laser (i.e., "the photochemical reaction [cannot be used with] ... continuous [wave lasers]").

Daikuzono appears to be silent with regard to specific photochemical reactions suitable with the described apparatus, but notes in the Background of the Invention that:

> ... Dougherty et al reported in 1978 about [thermotherapy] that when *hematoporphyrin derivatives* (HpD) were injected intervenously and weak beam of argon laser or argon pigment laser was irradiated after 48 hours, said HpD generated a first-order oxygen to show a strong carcinostatic activity.... It has also been known that *pheophobide a* is employable as a *photoreactive agent*. As a laser beam, there has been used YAG laser. (Col. 1, lines 32-43, emphasis added)

Applicants could find no disclosure of use for activation of endogenous photosensitizers. Thus, the disclosure concerning use of the apparatus in Daikuzono is limited to use with exogenous photosensitizers (i.e., hemotoporphyrin derivative and pheophorbide a, both of which are exogenous photosensitizers).

Therefore, Daikuzono clearly does not disclose all the elements of independent claim 55 of the present application.

In the Office Action, the Examiner acknowledges that Daikuzono does not disclose all of the features of the rejected claims of the present application. The Examiner, however, states:

> It would have been obvious ... to modify the wavelength and pulse duration to excite a specific photochemical reaction depending on the chemical present in the tissue, and to modify the length of the probe to reach the target area of tissue.[2]

In contrast to the teaching in Daikuzono, amended Claim 55 of the present application recites that treatment of certain tissues is effected by "non-invasively treating the particular volume of tissue with light." This feature is illustrated by the specification and accompanying drawings of the present application,[3] which teach a non-invasive method for treatment of a certain volume of tissue containing an endogenous pigment.

---

[2]This statement appears to be acknowledging that, if one of skill in the art were contemplating use of the teachings in Daikuzono to treat subsurface tissues, such practitioner would be lead to use an invasive probe wherein such probe would be made of a length appropriate to reach into such tissue.

[3] The Examiner's attention is, in particular, directed to Figures 9 and 10 of the present application, which illustrate use of a focused light beam or a non-focused light beam, respectively, to thermally overload and kill pigmented tumor cells. Attention to the specification at Page 23, line 19 - page 26, line 20, will provide the Examiner with further insight into the non-invasive methods and apparatus of the present invention.

Further, whereas Daikazono teaches certain uses of a thermotherapy apparatus in conjunction with an exogenous photosensitizer[4], the claimed invention utilizes endogenous photosensitizers.

Accordingly, it is respectfully submitted that Daikuzono, in all critical regards, teaches away from the method of amended Claim 55. In particular, whereas Daikuzono's thermotherapy apparatus constitutes an *invasive means* for delivering therapeutic energy to *unspecified tissue*, the method of Claim 55 constitutes a *selective means* for *non-invasive delivery* of therapeutic energy to *specific tissues* (i.e., pigmented tissues). In fact, Applicants believe that the apparatus in Daikuzono must be inserted directly into the tissue to be treated because physical proximity to the probe tip provides the only means for achieving selectively with regard to tissue destruction. Further, whereas Daikuzono requires use of an exogenous photosensitizer, the method of Claim 55 utilizes naturally occurring endogenous photosensitizers.

Hence, since Daikuzono does not disclose or suggest the claimed method but instead actually teaches away from the claimed method in so many key regards, Applicants believe that it is highly unlikely that one skilled in the art would arrive at the claimed invention upon reading the disclosure in Daikuzono. Accordingly, Applicants respectfully request that the Examiner's rejection of Claims 55-69 under U.S.C. 102(b) or U.S.C. 103(a) over Daikuzono be withdrawn.

B. Rejection Over Chen, et al.

The Examiner further rejects Claims 55, 56, 68, 69, and 71 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (USP 5,445,608). Applicants also rigorously but respectfully traverse this rejection for a number of reasons, as discussed below.

---

[4] Daikazono only mentions use of hematoporphyrin derivative and pheophorbide a, both examples of exogenous photosensitizers.

As discussed *supra*, Claim 55 of the present application is directed to a non-invasive method for the treatment of a particular volume of tissue containing an endogenous pigment, using light to promote thermal overload of pigmented cells to kill the pigmented cells. As explained in detail below, Chen et al. fails to disclose or suggest many of these features, such as for example, non-invasive treatment or use of an endogenous pigment (as the Examiner admits).

More specifically, Figures 2A-2C illustrate that the method and apparatus in Chen et al. concern use of an *invasive light application device* (i.e., catheter) for photodynamic therapy. Moreover, such photodynamic therapy is effected using an *exogenous photosensitizer*. In the Abstract, Chen et al. states:

> Light developed by an *implantable probe* is used to illuminate a treatment site that *has been perfused with a photoreactive agent*. A number of different embodiments of implantable probes are disclosed. (Abstract, emphasis added)

The Field of the Invention in Chen et al. confirms this limitation:

> This invention generally relates to a method and apparatus for photodynamic therapy of tissue by light irradiation, and more specifically, to a *method and apparatus for supplying light to a treatment site that has selectively absorbed a photoreactive agent perfused into it*, for example, to selectively destroy cancerous cells. (col. 1, lines 6-12)

Further, it is clear from the Background of the Invention that such photodynamic therapy, as envisioned in Chen et al., involves activation of an exogenous photosensitizer. Specifically, the reference defines PDT in the following way:

> A tumor comprising abnormal cells is known to *selectively absorb certain dyes perfused into the site* to a much greater extent than surrounding tissue.... *Once pre-sensitized by dye tagging*, the cancerous or abnormal *cells can be destroyed by irradiation with light* of an appropriate wavelength or waveband *corresponding to an absorbing wavelength or waveband of the dye*, with less damage to normal tissue. *This procedure*, which *is known as photodynamic*

> *therapy* (PDT), has been clinically used [for treatment of a number of diseases].... Because PDT may be selective in destroying abnormal cells that have absorbed more of the dye, it can successfully be used to kill malignant tissue with less effect on surrounding benign tissue in the brain and other critical areas. (col. 1, lines 15-36, emphasis added)

Thus, Chen et al. defines PDT as activation of an applied dye (i.e., perfusion of an exogenous photosensitizer into a site, such as a tumor). Further insight into the role of exogenous photosensitizers in Chen et al. is provided by the following:

> The theoretical basis behind PDT is that the *light energy absorbed by dye molecules* in the malignant cells *is transferred to dissolved oxygen to produce a reactive species called "singlet oxygen."* This highly reactive form of oxygen kills cancer cells and damages tumor vasculature.... Contrary to the teachings of most of the prior art, the effectiveness of each photon of light impacting the treatment area may be highest at very low light intensities, over extended treatment times, and the optical efficiency may in fact decrease with increasing exposure level. (col. 1, line 59 - col. 2, line 10, emphasis added)

Hence, Chen et al. has narrowly defined PDT to encompass activation of exogenous photosensitizers that, upon activation, produce singlet oxygen. Thus, the reference effectively limits the scope of its disclosure to this subset of photosensitizing compounds.

As noted by the Examiner, Chen et al. does mention using a thermal component in their PDT treatment. However, contrary to the Examiner's apparent interpretation, such use of thermal energy in Chen et al. is solely to augment the effects of PDT upon activation of the exogenous photosensitizer. Specifically, the passage cited by the Examiner reads:

> *For all PDT light sources*, the vast majority of the *optical power* delivered to tissue eventually *degrades to heat*. From a therapy perspective, it is likely that *this heat load will augment the treatment* due to improved chemical reaction rates at higher tissue temperatures. It is also true that cells kept above approximately 43° C are not viable. This effect is, in fact, used in the treatment of cancer using *hyperthermia*. In that situation, an attempt is made to *heat the target tumor with radio frequency energy* to a temperature on the

> order of 43°-45° C, while maintaining surrounding healthy tissue below 43° C. *Combining hyperthermia with conventional transcutaneous PDT* has been shown by B. Henderson et al. to increase the efficacy of both treatments.... *Combining hyperthermia treatment with PDT delivered*, for example, *by an implantable probe* in accordance with the present invention, will very likely augment the effects of either treatment used alone in destroying tumors. (col. 3, line 6-27, emphasis added)

Thus, Chen et al. discloses that a by-product of conventional PDT regimens is heating of treated tissue, and that such heating may enhance the effects of PDT. Chen et al. also discloses use of heat alone to treat tissue, albeit through reference to other's application of radiofrequency energy (not light energy) to effect such heating. Finally, Chen et al. states that the method and apparatus disclosed therein may be suitable for PDT wherein such PDT is combined with localized heating of the treated tissue.

Conspicuously absent from this is any disclosure of selective tissue heating using a non-invasive light-based method, or heating of tissue using light in the absence of a PDT photosensitizer (since, as described *supra*, per Chen et al., PDT comprises activation of an exogenously applied photosensitizer).

Chen et al. continues this disclosure in the Summary of the Invention, which starts by stating:

> In accordance with the present invention, a *method for photodynamic treatment at an internal, in vivo treatment site* to cause a desired therapeutic change *comprises* the step of *applying a photoreactive agent* that is selected for its characteristic wavelength(s) or waveband(s) of light absorption to the internal, in vivo treatment site. *A light source* having one or more emission wavelengths or wavebands substantially equal to an absorbing wavelength or waveband of the photoreactive agent *is then positioned internally within a patient's body*. Light emitted from the light source is then administered directly to the internal, in vivo treatment site and is absorbed by the photoreactive agent, which causes the desired therapeutic change at the treatment site. (col. 3, line 57 - col. 4, line 2, emphasis added)

Therefore, the disclosure and invention in Chen et al. appears to be limited to PDT with an applied (i.e., exogenous) photosensitizer, wherein such photosensitizer is activated using an implanted or otherwise interstitial light source. This is subsequently expanded to include heating of PDT-treated tissue by the following disclosure in Chen et al.:

> A further step in the method is to *heat the treatment site to improve the efficacy of the photodynamic treatment.* The step of heating may then comprise the step of using waste heat from the source of light that is disposed proximate to the treatment site. (col. 5, lines 1-5, emphasis added)

Hence, any such heating is a by-product of the PDT regimen using an exogenous photosensitizer and implanted light source. Also, any such heating is clearly linked to the PDT process, and is not used outside the context of PDT.

Applicants respectfully submit that the independent claims in Chen et al. support these inherent limitations in the teachings in Chen et al.[5] Specifically, Claim 1 recites:

> Claim 1. A *method for photodynamic treatment* at an internal, in vivo treatment site, to cause a desired therapeutic change, comprising the steps of:
> (a) *applying a photoreactive agent to the internal, in vivo treatment site*, said photoreactive agent being selected for one or more characteristic wavelengths or wavebands of light absorption;
> (b) *positioning a light source that directly generates light internally within a patient's body*, said light source being transcutaneously delivered to the in vivo treatment site and left implanted within the patient's body during the photodynamic treatment, the light emitted by the light source having one or more emission wavelengths or wavebands substantially equal to a wavelength or waveband of absorption of the photoreactive agent; and
> (c) administering the light emitted from the light source to the internal, in vivo treatment site, said light being absorbed by the photoreactive agent, which then causes the desired therapeutic change at the treatment site.

---

[5] While Applicants acknowledge that the reference is not limited to what is claimed therein, the claims do provide a good indication of the subject matter disclosed in this reference.

Thus, Claim 1 requires use of an exogenous photosensitizer (the photoreactive agent) and an implanted light source. In similar fashion, Claims 47, 49, 58, and 59 concern related methods for PDT using exogenous photosensitizers and implanted light sources:

> Claim 47. A *method for photodynamic treatment* at an internal, in vivo treatment site in a patient's body, to cause a desired therapeutic change, comprising the steps of:
> (a) exposing the internal, in vivo treatment site, so that it is accessible from outside the patient's body;
> (b) *applying a photoreactive agent* to the internal, in vivo treatment site, said photoreactive agent being selected for a characteristic wavelength or waveband of light absorption;
> (c) *transcutaneously implanting a light source* proximate to the treatment site, said light source having an emission wavelength or waveband substantially equal to a wavelength or waveband of light absorption of the photoreactive agent;
> (d) closing the light source inside the patient's body; and
> (e) administering light to the treatment site from the light source, said light being absorbed by the photoreactive agent, which then causes the desired therapeutic change.

Therefore, Claim 47 also clearly requires use of an exogenous photosensitizer and an implanted light source.

> Claim 49. A method for at an internal, in vivo treatment site in a patient's body, to cause a desired therapeutic change, comprising the steps of:
> (a) *applying a photoreactive agent* to the internal, in vivo treatment site, said photoreactive agent being selected for at least one characteristic wavelength or waveband of light absorption;
> (b) providing an *array of individually addressable light emitting devices that are spaced apart from the internal, in vivo treatment site*, said light emitting devices having at least one predefined emission wavelength or waveband as required for the photodynamic treatment; and
> (c) administering light to the internal, in vivo treatment site from the array of light emitting devices by selectively energizing specific ones of the light emitting devices to achieve a desired pattern of light illuminating the treatment site, said light causing the desired therapeutic change.

Although the precise location of the "array of individually addressable light emitting devices" is ambiguous in Claim 49, Applicants believe that one of ordinary skill in the art would conclude that this array, based on the drawings and other disclosures made in the specification of Chen et al., is implanted directly within the body or provides light that is conducted into the body *via* implanted light guides (such as fiberoptic catheters).

> Claim 58. A *method for photodynamic treatment at a treatment site in a patient's head*, said treatment site including at least one of a sinus cavity, a nasal pharyngeal surface, a mouth surface, a throat surface, and an inner aural surface, to cause a desired therapeutic change, comprising the steps of:
> (a) *applying a photoreactive agent to the treatment site* inside the patient's head, said photoreactive agent being selected for at least one characteristic wavelength or waveband of light absorption;
> (b) *positioning a light source proximate to the treatment site* to illuminate the treatment site both internally and externally of the patient' s head, said light source having at least one emission wavelength or waveband substantially equal to a wavelength or waveband of absorption of the photoreactive agent; and
> (c) administering light to the treatment site from the light source, said light being absorbed by the photoreactive agent, which then causes the desired therapeutic change.

Hence, Claim 58 recites both application of an exogenous agent within the body and positioning a light source proximate to this internal treatment site. Based on the disclosures in the specification of Chen et al., Applicants again submit that one of ordinary skill in the art would be led to conclude that such positioning requires implantation or other insertion of such light source into the body such that it is made proximate to such treatment site, and such that illumination of locations within the patient's head can be effected.

> Claim 59. A *method for photodynamic treatment* at an internal, in vivo treatment site, to cause a desired therapeutic change, comprising the steps of:

(a) *applying a photoreactive agent* to the internal, in vivo treatment site, said photoreactive agent being selected for one or more characteristic wavelengths or wavebands of light absorption;
(b) *positioning a light source internally within a patient's body*, said light source being transcutaneously delivered to and implanted at the in vivo treatment site, said light source emitting a light having one or more emission wavelengths or wavebands substantially equal to a wavelength or waveband of absorption of the photoreactive agent;
(c) electromagnetically coupling power from an external power source to the light source to energize the light source during the photo dynamic treatment without directly connecting the external power source to the light source via a conductor; and
(d) administering light emitted flora the light source to the internal, in vivo treatment site, said light being absorbed by the photoreactive agent, which then causes the desired therapeutic change at the treatment site.

Thus, Claim 59, like each of the other method claims, clearly requires use of an exogenous photosensitizer and an implanted light source.

Similar to the method claims in Chen et al., the apparatus claims therein also include the same limitations. More specifically, apparatus Claim 20 (like method Claim 1), concerns photodynamic treatment using an implanted light source. This claim also includes heating of the treatment site as a by-product of such PDT:

Claim 20. Apparatus for administering *photodynamic treatment* at an internal, in vivo treatment site, to cause a desired therapeutic change, comprising:
(a) a light source having at least one characteristic emission wavelength or waveband suitable for the photodynamic treatment;
(b) *a supporting structure for said light source, said supporting structure being adapted for invasive disposition within a patient's body*, to support the light source proximate to said internal, in vivo treatment site, shaped to administer light generated by the light source directly to said treatment site from the light source without conveying the light over an optical fiber from a point external to the patient's body, and *adapted to be inserted transcutaneously and implanted* during the photodynamic treatment, allowing said light source to be selectively energized to directly irradiate the internal, in vivo treatment site with said light, to cause the desired therapeutic change at the treatment site, *heat produced by the light source* being

absorbed by the treatment site to *improve the efficacy of the photodynamic treatment*; and
(c) a power supply that provides an electrical current to energize the light source.

As recited by Claim 20, any heating of the treatment site is a direct consequence of the presence and activation of the implanted light source within such treatment site.

Claim 48. Apparatus for administering a *photodynamic treatment* at an internal, in vivo treatment site, to cause a desired therapeutic change, comprising:
(a) a light source having at least one emission wavelength or waveband substantially equal to a predefined light absorption wavelength or waveband required for the photodynamic treatment;
(b) a supporting structure for said light source, said supporting structure being *adapted to be invasively transcutaneously implanted* and left enclosed within a patient's body, proximate said internal, in vivo treatment site, and shaped to administer the light directly to the internal, in vivo treatment site, light emitted by the light source causing said desired therapeutic change; and
(c) a power supply that provides an electrical current to energize the light source without using conductors extending outside of the patient's body in which the light source is implanted.

Hence, Claim 48 also clearly describes an implanted light source for PDT.

Claim 53. *Apparatus for photodynamic treatment* of an internal, in vivo treatment site to cause a desired therapeutic change, comprising:
(a) an *array of individually addressable light emitting devices* that are spaced apart from the internal, in vivo treatment site, said light emitting devices each having at least one predefined emission wavelength or waveband required for the photodynamic treatment;
(b) means for selectively energizing specific ones of the light emitting devices at a time to emit light that illuminates the internal, in vivo treatment site, to cause the desired therapeutic change; and
(c) a power supply that is coupled to the means for selectively energizing, to supply electrical current to energize the specific ones of the light emitting devices in the array.

As with Claim 49, the precise location of the "array of individually addressable light emitting devices" recited in claim 53 is ambiguous. However, in light of the wording in the claim, Applicants believe that one of ordinary skill in the art would conclude that this array, based on the drawings and

other disclosures made in the specification in Chen et al., is implanted directly within the body or provides light that is conducted into the body *via* implanted light guides (such as fiberoptic catheters).

> Claim 61. *Apparatus for administering photo dynamic treatment* at an internal, in vivo treatment site, to cause a desired therapeutic change, comprising:
> (a) *a light source* having at least one characteristic emission wavelength or waveband suitable for the photodynamic treatment;
> (b) a *supporting structure for said light source*, said supporting structure being *adapted for invasive disposition* within a patient's body, to support the light source proximate to said internal, in vivo treatment site, shaped to administer light directly to said treatment site from the light source, and adapted to be inserted transcutaneously and left in place during the photodynamic treatment, allowing said light source to be selectively energized to irradiate the internal, in vivo treatment site with said light, to cause the desired therapeutic change at the treatment site;
> (c) an external power source for supplying an electrical current to a transmitter that is adapted to be positioned externally adjacent a patient's body, proximate the treatment site; and
> (d) a receiver that is adapted to be implanted within the patient's body and coupled to the light source disposed at the treatment site, said transmitter electromagnetically coupling the electrical current produced by the external power source to the receiver, to induce an electrical current to flow in the receiver for energizing the light source.

Thus, Claim 61 clearly describes an implanted light source for PDT.

After careful scrutiny of the specification and claims of Chen et al., Applicants fail to find support for the Examiner's assertion that the claimed invention would have been obvious because, as alleged by Examiner, "it would have been obvious to one of ordinary skill in the art at the time of the invention to use either an exogenous or an endogenous photodynamic chemical for PDT." First, Chen et al. fails to teach treatment of pigmented tissues using optical energy, with or without

a photosensitizer.[6] Second, Chen et al. fails to teach treatment of pigmented tissues using optical energy alone.[7] Third, Chen et al. fails to teach treatment of any tissue using only non-invasive,

---

[6] As explained in the specification for the present application, the special optical properties of such pigmented tissues necessitate use of special methods and apparatus for successful treatment of such tissues. These special methods and apparatus are lacking in the teachings of Chen et al. For example, Chen et al. make no mention of optical factors, such as absorption or scatter, affecting light penetration into pigmented tissues, nor of any means for circumventing the possibly deleterious effects of such factors upon effective light delivery into such pigmented tissues.

[7] As explained in the specification for the present application, the special optical properties of such pigmented tissues allow special methods and apparatus to be used for successful treatment of such tissues without requiring application of an exogenous photosensitizer. Cognizance of these special methods and apparatus is lacking in the teachings of Chen et al. For example, Chen et al. makes no mention of photochemically active species, such as 5-SCD or melanin, naturally present in some such pigmented tissues, nor of any means for harnessing the therapeutic potential of such endogenous species when treating such pigmented tissues.

externally applied optical energy.[8] And fourth, Chen et al. fails to teach treatment of pigmented tissues using light-induced thermal overload alone.[9]

The method of amended independent Claim 55 is clearly distinct from that which is disclosed or suggested in Chen et al. In particular, features, such as non-invasive treatment of tissue containing an endogenous pigment in the claimed invention, are clearly not disclosed or suggested by, and distinguish the claimed invention, from that which is disclosed in Chen et al. Accordingly, Applicants request withdrawal of the Examiner's rejection of Claims 55 56, 68, 69 and 71 under 35 U.S.C. 103(a) over Chen et al.

C. Rejection Over Talmore

Finally, the Examiner has rejected Claims 55- 75 under 35 U.S.C. 102(e) as being anticipated or, in the alternative, under 35 U.S.C. 103(a) as obvious over Talmore (USP 5,707,401). For substantially the same reasons discussed above for Daikuzono and Chen et al., Applicants vigorously but respectfully traverse this rejection.

More specifically, Talmore discloses an apparatus for increasing the efficiency of standard PDT through the simultaneous application of light energy so as (1) to activate an applied

---

[8] Chen et al. requires insertion or implantation of light delivery apparatus directly into or proximal to tissues to be treated. In contrast, the present application teaches special non-invasive methods and apparatus that can be used for successful treatment of tissues without requiring invasive positioning of a light applicator.

[9] Chen et al. requires use of an exogenous photosensitizer in conjunction with any thermal effects, and in particular characterizes such thermal effects as augmenting PDT. In contrast, the present application teaches special non-invasive methods and apparatus that can be used for successful treatment of tissues solely through light-induced thermal overload of pigmented tissues.

photosensitizer and (2) to produce localized hyperthermia. Specifically, in the Abstract, Talmore states:

> The present invention relates to an improved apparatus for a therapeutic treatment of malignant solid tumors, consisting of a *combined photodynamic therapy and hyperthermic treatment....* (Abstract, emphasis added)

That the apparatus is for PDT is stated at the outset of the specification (in what is usually termed the Field of the Invention):

> The present invention relates to an apparatus for invivo treatment of tumors. More particularly, the invention relates to an improved apparatus for an efficient photodynamic therapy as an in-vivo treatment of tumors. (Col. 1, lines 4-7)

Talmore then defines what is meant by PDT in the Background of the Invention:

> Photodynamic Therapy (hereinafter referred to as PDT) ... is based on a *systemic or topical administration of a tumor-localizing photosensitizer reagent*, such as porphirin, aminolevulinic acid (ALA), phtalocyanin, chlorine etc., which after illumination and excitation with visible light in the presence of oxygen, gives rise to highly reactive and cytotoxic singlet molecular oxygen which leads to tumor regression .... (Col. 1, lines 10-19, emphasis added)

Thus, it is clear that by PDT, Talmore means a therapeutic method involving application of an exogenous photosensitizer capable of supporting photocatalytic generation of singlet oxygen.

The apparatus in Talmore is subsequently described as follows in the Brief Description of the Invention:

> The invention relates to an efficient apparatus for a therapeutic treatment of malignant solid tumors, consisting of a *combined photodynamic therapy and hyperthermic therapy* ... (Col. 2, lines 40-43, emphasis added)

The requirement, according to Talmore, of simultaneous PDT and hyperthermia is further emphasized by independent Claim 1 in Talmore:

> Claim 1. An apparatus for an efficient *simultaneous photodynamic and hyperthermic treatment* .... (emphasis added)

Thus, Talmore discloses an apparatus for simultaneous photoactivation of an applied photosensitizer and production of hyperthermia at such PDT treatment site.

In so far as Talmore describes the optical properties of tissue,[10] such description is limited to the role of oxyhemoglobin and a purported thermally-induced release of oxygen for augmenting the efficacy of PDT.[11] In fact, Applicants fail to find any discussion or disclosure of any direct role of pigments (i.e., melanin) in any aspect of the alleged invention in Talmore.

In contrast to the teachings in Talmore, which require application of an exogenous photosensitizer, the claimed invention is directed to a method which is useful for selective destruction of pigmented tissues through direct application of light to unadulterated tissues. Further, whereas Talmore apparently avoids use of optical wavelengths that might interact with such pre-existing pigments, the claimed method is useful for selective destruction of such pigmented tissues through use of interaction with such pigments.

More specifically, amended independent Claim 55 of the present application recites:

> Claim 55. (amended) A method for the treatment of a particular volume of tissue, said volume of *tissue containing an endogenous pigment*, the method comprising the steps of:

---

[10] While Talmore carefully illustrates in Fig. 2 that certain tissue components have unique optical properties, the reference makes no mention of use of such properties for selective thermal destruction of pigmented tissues.

[11] See, for example, Talmore's disclosure at Col. 4, lines 36-48, which concerns purported release of oxygen from hemoglobin upon irradiation of such hemoglobin at wavelengths between 600-750 nm.

non-invasively *treating* the particular volume of *tissue with light to promote thermal overload of pigmented cells* in the particular volume of tissue, wherein said thermal overload kills said pigmented cells. (The italics are for emphasis, not to show amendments)

This is in clear contrast to the disclosure in Talmore, which uses hyperthermia to augment the effects of PDT with an exogenous photosensitizer.

In addition, Talmore does not disclose or suggest use of non-linear excitation methods, as recited in Claim 75 of the present application. Although Talmore teaches simultaneous illumination of tissue at several wavelengths, such illumination conditions are incapable of promoting two-photon excitation of any photosensitizer contained in such tissue. Further, such simultaneous illumination is intended solely to yield concurrent photoactivation of an applied photosensitizer (via a conventional single-photon excitation process) and production of hyperthermia. As described in the present application, two-photon excitation requires special illumination conditions that simply cannot be provided by the apparatus of Talmore. Further, Talmore makes no disclosure concerning any possible use of two-photon excitation methods.

Therefore, Applicants respectfully submit that Talmore does not anticipate nor render obvious the method claimed in the rejected claims, since numerous key elements of the claimed invention are absent from the teaching in Talmore. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of independent Claims 55 and 75(and of all claims dependent thereupon) based on 35 U.S.C. 102(e) or 35 U.S.C. 103(a) over Talmore.

D. Conclusion on 102/103 Rejections

For the above-stated reasons, it is respectfully submitted that the rejections over the art have been overcome. Accordingly, it is requested that these claims now be allowed.

III. ALLOWABLE SUBJECT MATTER

The Examiner has stated that Claims 75-77 are allowed. The Examiner further has stated that Claims 1-36 and 97-107 contain allowable subject matter. As the double patenting rejection of these claims has now been overcome, it is requested that these claims be allowed. Further, as Claims 37-54 are only rejected under the double patenting rejection, it is requested that they now be allowed.

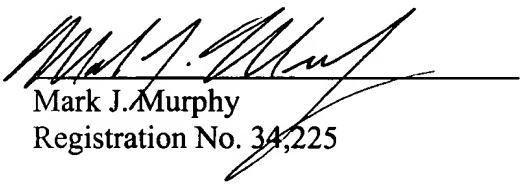
Conclusion

For the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable condition and are neither disclosed nor suggested by the cited reference and are patentable thereover. Accordingly, it is requested that the claims be passed to allowance.

If any fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,



Mark J. Murphy
Registration No. 34,225

COOK, ALEX, McFARRON, MANZO,
CUMMINGS & MAHLER, Ltd.
200 West Adams Street-Suite 2850

Chicago, Illinois 60606
(312) 236-8500